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CHAPTER 8

Novelty processing and memory formation in Parkinson's disease

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Abstract

BACKGROUND: Parkinson's disease (PD) is characterized by a degeneration of nigrostriatal dopaminergic cells, resulting in dopamine depletion. This depletion is counteracted through dopamine replacement therapy (DRT). Dopamine has been suggested to affect novelty processing

and memory, which suggests that these processes are also implicated in PD and that DRT could affect them.

OBJECTIVE: To investigate word learning and novelty processing in patients with PD as indexed by the P2 and P3 event-related potential components, and the role of DRT in these processes.

METHODS: 21 patients with PD and 21 matched healthy controls were included. Patients with PD were tested *on* and *off* DRT in two sessions in a counterbalanced design, and healthy controls were tested twice without intervention. Electroencephalogram (EEG) was measured while participants performed a word learning Von Restorff task.

RESULTS: Healthy controls showed the typical Von Restorff effect, with better memory for words that were presented in novel fonts, than for words presented in standard font. Surprisingly, this effect was reversed in the patients with PD. In line with the behavioral findings, the P3 was larger for novel than for standard font words in healthy controls, but not in patients. For both groups the P2 and P3 event-related components were larger for recalled versus forgotten words. DRT did not affect these processes.

CONCLUSIONS: Learning of novel information is compromised in patients with PD. Likewise, the P2 and P3 components that predict successful memory encoding are reduced in PD patients. This was true both on and off DRT, suggesting that these findings reflect abnormalities in learning and memory in PD that are not resolved by dopaminergic medication.

Introduction

Dopaminergic neurons are known to be activated by reward-related and salient stimuli that are relevant, arousing or alerting to the observer (Schultz, 1992; Chiodo, Antelman, Caggiula, & Lineberry, 1980; Contreras-Vidal & Schultz, 1999; Strecker & Jacobs, 1985), but also to high intensity (Horvitz, Stewart, & Jacobs, 1997) and unexpected stimuli (Schultz, 1998). In particular, dopaminergic neurons are known to respond with a fast increase in bursts of spikes (a phasic dopamine response) to novel but not familiarized stimuli in awake monkeys (Ljungberg, Apicella, & Schultz, 1992; Ljungberg, Apicella, & Schultz, 1991) and cats (Steinfels, Heym, Strecker, & Jacobs, 1983), even when the novel information is not motivationally significant or explicitly rewarding (Horvitz, 2000). These responses often go together with overt orienting behavior consisting of eye and body movements towards the novel stimuli; however, such overt behavioral responses are no prerequisite to evoke the responses of dopaminergic neurons (Schultz, 1992). Dopaminergic neurons thus respond to salient novel information, but relatively little is known about the functional role of dopamine in processing novel information. However, one role has been suggested in an influential model: A novelty signal originating from the hippocampus may enhance memory encoding through a functional loop between the hippocampus and the substantia nigra/ventral tegmental area promoting dopamine release (SN/VTA; Lisman & Grace, 2005). In the present study, the role of dopamine in processing and encoding of novel information was investigated in patients diagnosed with idiopathic Parkinson's disease (PD) and healthy subjects.

PD is characterized by a degeneration of dopaminergic cells in the SN pars compacta that project to the dorsal striatum (Betchen & Kaplitt, 2003). Consequently, dopamine is depleted especially in the dorsal striatum of patients with PD. The ventral striatum may already be affected at an early stage, but to a lesser extent (Vriend et al., 2014). Dopamine depletion in the dorsal striatum leads to prominent motor symptoms, such as rigidity, bradykinesia and tremor. Dopamine replacement therapy (DRT) is mostly aimed at ameliorating these symptoms (Bodis-Wollner, 2010a, 2010b). In addition, PD is also characterized by cognitive impairments. For example, patients suffer from an impairment in executive functioning similar to that in patients with frontal lobe damage (Kehagia, Barker, & Robbins, 2010; Lewis, Dove, Robbins, Barker, & Owen, 2003; Owen, 2004; Owen et al., 1992; Taylor, Saint-Cyr, & Lang, 1986), and also suffer from memory deficits. In particular, episodic recall is impaired, while recognition memory may be relatively spared (Brown, & Marsden, 1987; Buytenhuijs et al., 1994; Fischer et al., 1990; Helkala, Laulumaa, Soininen, & Riekkinen, 1988; Mohr et al., 1989; Sagar, Sullivan, Gabrieli, Corkin, & Growdon, 1988; Sullivan & Sagar, 1989; Taylor et al., 1986; Tweedy, Langer, & McDowell, 1982; Weingartner, Burns, Diebel, & LeWitt, 1984).

Although cognitive problems (e.g. with learning and memory) have also been associated with abnormalities in other neurotransmitter systems, such as cholinergic (Narayanan, Rodnitzky, & Uc, 2013) and glutamatergic pathways (Borbely, Scheich, & Helyes, 2013), it is most often associated with alterations in dopaminergic brain circuits (Lewis et al., 2003; Owen, 2004), on which we will focus on dopamine in the present study. Brain imaging studies (Dagher, 2001; Owen, Doyon, Dagher, Sadikot, & Evans, 1998; Sawamoto, et al., 2008) and animal studies (Chao, Pum, & Huston, 2013) have suggested that the cognitive problems (e.g. memory deficits) in PD patients are caused by deficits in the dopaminergic forebrain projections, especially of nigrostriatal dopamine. Aggleton and Brown's (1999) model suggests that recall depends on the hippocampus and its direct connections with the diencephalon, whereas familiarity-based recognition depends on an independent network including the perirhinal cortex, thalamus, and frontal cortex. Hippocampal functioning has been suggested to depend heavily on dopamine (Benchenane et al., 2010; Lisman & Grace, 2005), and is therefore vulnerable to dopamine depletion, whereas this does not seem be the case to the same extent for perirhinal functioning. This could explain why recall is affected to a larger degree than recognition in Parkinson's disease. However, frontal cortex dysfunction is also known to result mostly in recall deficits (Blum, Hebert, & Dash, 2006; Pergola & Suchan, 2013). It is thus still unclear whether these problems are caused by the depletion of dopamine in the nigrostriatal pathway or by frontal cortex dysfunction, or an interaction between the two (Chao, et al., 2013).

Novelty processing is believed to depend on dopamine (Lisman & Grace, 2005; Rangel-Gomez et al., 2013), and therefore may be impaired in patients with PD, especially when off dopaminergic medication. Novelty processing could therefore function as a marker for the extent to which memory deficits depend directly on the dopaminergic system. To study novelty processing and memory encoding in PD, we used a Von Restorff task (Von Restorff, 1933) that has previously been found to be sensitive to dopamine challenge in young adults (Rangel-Gomez et al., 2013). In this task participants study words that are presented in either novel fonts, or in a standard font. Words presented in a novel font and/or deviant color are often remembered better than the words presented in a standard font; this effect is known as the Von Restorff effect (Von Restorff, 1933), and also as the isolation - or distinctiveness effect (Bruce & Gaines, 1976; Dunlosky et al., 2000; Geraci & Manzano, 2010; Geraci & Rajaram, 2004; Rangel-Gomez et al., 2013; Rangel-Gomez & Meeter, 2013; Schmidt, 1985).

We also recorded the electroencephalogram (EEG) in order to collect psychophysiological measures. This task and the EEG measures allowed us to investigate the differences between patients with PD and healthy controls on two processes: First, on episodic encoding, and second on novelty processing. Of main interest were the P2 and P3 event-related potential (ERP) components elicited by the words during encoding. The P2 is a positive component peaking around 150 and 275 ms post-stimulus, which has been reported to peak at posterior electrode sites in learning and visual priming tasks (Freunberger, Klimesch, Doppelmayr, & Holler, 2007; Rushby, Barry, & Johnstone, 2002). It has been suggested to reflect a cognitive matching process crucial to identify elements in the sensory input that are new and different from stored representations (Freunberger et al., 2007). In indexes elaborative learning of words - its amplitude predicting subsequent recall (Rushby et al., 2002). Therefore, we expected an enhanced P2 for remembered versus forgotten words. In addition, the P2 is associated with the motivational salience of stimuli defined by their task relevance or novelty (Riis et al., 2009), therefore, it was expected that the P2 component would be larger for novel than for standard font words during encoding.

The second component of interest is the P3. Deviant or novel stimuli sometimes elicit two distinctive peaks in the P3 time window, between 300 and 475 ms post stimulus onset, that have been functionally dissociated (Polich, 2007). The first, referred to as the P3a, typically peaks frontocentrally (Simons et al., 2001) with an assumed frontal origin (Polich, 2007); the second, known as the P3b, peaks more posteriorly (Courchesne et al., 1975; Polich & Criado, 2006; Soltani & Knight, 2000; N. K. Squires et al., 1975), and is believed to originate from temporal or parietal regions (Polich, 2007). The more anterior P3a is believed to reflect an involuntary shift of attention in an evaluative stage of processing novel information (Friedman et al., 2001; Ranganath & Rainer, 2003). The main determinant for P3b amplitude has been associated with task relevance (Gaeta, Friedman, & Hunt, 2003; Kazmerski & Friedman, 1995). It is believed to reflect updating of working memory (Courchesne et al., 1975), and it has been implicated in memory processing in general (Polich, 2007). In the Von Restorff effect, the P3 is typically larger for the deviant stimuli; sometimes its size is found to correlate with the size of the Von Restorff effect (Fabiani & Donchin, 1995; Fabiani, Karis, & Donchin, 1990; Kamp, Brumback, & Donchin, 2013; Karis, Fabiani, & Donchin, 1984; Otten & Donchin, 2000; Wiswede, Russeler, Hasselbach, & Munte, 2006), though others have not found this (Rangel-Gomez & Meeter, 2013). In addition, several studies have shown that the P3 amplitude during encoding predicts subsequent recall (Fabiani et al., 1990; Kamp et al., 2013; Karis et al., 1984).

In the literature, there are some hints that the P2 component may be affected by dopamine, as it is delayed in patients with PD (Antal et al., 2003), and in individuals with higher dopamine efficacy larger P2 amplitudes have been observed (Hammerer et al., 2013). The effect of dopamine on the P3 are equivocal. Higher levels of dopamine have been reported to reduce the P3 amplitude (Albrecht, Martin-Iverson, Price, Lee, & Iyyalol, 2011; Rangel-Gomez et al., 2013; Takeshita & Ogura, 1994), others found enhancements (Heitland et al., 2013), while others did not find any effects (Halliday et al., 1994; Nishimura, Ogura, & Ohta, 1995; Oranje et al., 2006). Also in patients with PD the results have been inconclusive. Some reporting a reduction in P3 in an off relative to an on DRT session (Mathis et al., 2014; Solis-Vivanco et al., 2011), or compared to healthy controls (Pulvermuller et al., 1996; Sartucci et al., 1990). Others found the opposite, a

larger P3 while off DRT (Ruzicka, Roth, Spackova, Mecir, & Jech, 1994), and in patients with PD than in healthy controls (Green et al., 1996; Tanaka et al., 2000). Yet others reported no differences between patients and controls (Aragane, Tachibana, & Sugita, 1995; Toda, 1991; Wright, Geffen, & Geffen, 1996). Therefore, it remains unclear which role dopamine plays in the generation of the P2 and P3 components.

In the present study patients with PD and matched healthy controls performed the Von Restorff task twice. Patients were tested one morning after overnight withdrawal from DRT (the *off* session) and on a different morning around one hour after intake of DRT (the *on* session). In general, memory performance was expected to be lower in patients than in healthy controls. Moreover, given the role of dopamine in novelty processing, a smaller Von Restorff effect was expected in patients, and alterations in the P2 and P3 ERP components elicited by novel font words. Of main interest was whether these alterations in memory and novelty processing would be sensitive to dopamine status. If deficits in learning and novelty processing result from alterations in dopaminergic tone, differences between patients and controls would be expected to be larger in the *off* than in the *on* session. If, on the other hand, they are a function mostly of frontal dysfunction, they would be expected to be similar in both sessions.

Methods

Participants

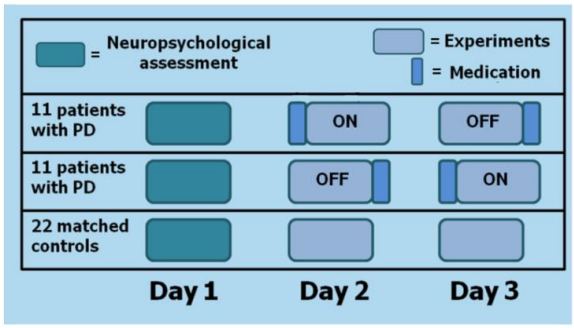
Twenty-one patients with PD (15 male; age 51-69, mean = 61.8), and 21 matched healthy controls (11 male; age 49-69, mean = 60.0) participated in the study. The patients were diagnosed with PD by a movement disorder specialist at the outpatient clinic from the VU University Medical Center in Amsterdam, the Netherlands according to the UK Parkinson's Disease Brain Bank criteria. All patients fell into Hoehn and Yahr stages 2-3 (Hoehn & Yahr, 1967), indicating bilateral involvement without notable impairment of balance. DRT consisted of either L-dopa monotherapy, dopamine agonist monotherapy, or a combination therapy of L-dopa and a dopamine agonist, with L-dopa equivalent daily dose (LEDD) ranging from 105-2800 mg (mean = 851.1 mg; SD = 581.1 mg; see Table 1 for details). LEDD was calculated using conversion as used by Olde Dubbelink, et al. (2013). Patients taking psychotropic and/or sedative medication, patients treated with deep brain stimulation, or patients with a current clinical diagnosis of a psychiatric disorder were excluded, as were patients and controls that scored lower than 24 on the Mini Mental State Examination (MMSE). The mean Schwab & England Activities of Daily Living score was 92, suggesting that the patients with PD still had complete independence, but experience some slowness, difficulty or impairment while performing daily activities. The mean Unified Parkinson's Disease Rating Scale (UPDRS) III score for patients with PD *on* was 21.8 and 29.1 *off* DRT.

The healthy controls were matched with patients with PD with respect to age, gender and educational level (Verhage, 1983). All participants received 90 Euros, reimbursement of travel expenses, plus a bonus of 20-40 Euros that could be earned in a reward task, and gave informed consent prior to participation. The study was performed in accordance with the ethical standards established in the Helsinki declaration and was approved by the local medical ethical committee.

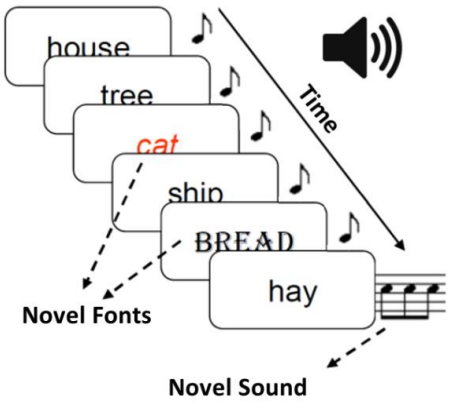
Table 1. *Medication*

Dopamine Replacement Therapy	
L-Dopa	*n* = 20 L-Dopa with carbidopa; L-Dopa with benserazide; L-Dopa with carbidopa and entacapon
Dopamine-agonists	*n* = 13 pramipexol (acting on D_2, D_3 and, D_4 receptors) pergolide (acting on D_1, and D_2 receptors).
LEDD	105 – 2800 mg (mean = 851.1, SD = 581.1)
Non-dopaminergic medication	Amantadine; rasagaline; entacapon; ropinirol; propranolol

LEDD = Levodopa Equivalent Daily Dose, was calculated for the combination of drugs taken by each participant.



A)



B)

Figure 1. *A) Shows the experimental design. B) Shows an example trial of the Von Restorff task (note, here example words in English, but the actual word lists consisted of Dutch words). Between words a fixation cross (not shown) was presented with a jittered duration of 500-1805 ms.*

Procedure

See Figure 1 for the experimental design. Patients with PD and healthy controls were tested on three separate occasions. The first day ('screening session') consisted of an extensive neuropsychological screening, including language tests, assessment of executive functioning, memory, and ratings of depression, anxiety, and impulsivity. The neuropsychological tests allowed checking whether matching was successful in terms of cognitive and affective functioning. The tests are described per category below. The screening took place in an examination room. In the two subsequent experimental sessions participants were tested in their homes, using a portable EEG set-up (128-channel ActiveTwo BioSemi system). Participants were seated behind a table in a room of their own choice with subdued lighting. EEG preparation and the Von Restorff task together took about 60 minutes. The entire session, including other tasks, breaks and the completion of the questionnaires, took about two and a half hours. The experimental sessions were conducted between seven and 50 days after the screening session, and at least one week apart.

Screening

Participants performed the 10-word learning list test of episodic memory (Spaan, 2003) to measure memory capacity for unrelated words. The Boston Naming Test (Kaplan, Goodglass, & Wintraub, 1983) and the category fluency test (for animals) were included to estimate basic visuospatial recognition, language skills, and size and speed of semantic retrieval, respectively. The Nederlandse Leesvaardigheidtest (NLV), the Dutch version of the National Adult Reading Test (Nelson, 1982), was used to estimate premorbid intelligence of the participants.

The Trailmaking Test (Delis, Kramer, Kaplan, & Holdnack, 2004; Tombaugh, 2004) and Tower of Hanoi (Delis, Kaplan, & Kramer, 2001) were used to estimate visual attention, mental flexibility, task switching abilities, motor speed and executive functioning. The MMSE was used to screen participants for dementia (a score of 24 or lower was an exclusion criterion) and to estimate overall cognitive functioning at time of the screening.

To assess anxiety and depression the Dutch versions of the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988) and the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) were used. These lists were also completed on the other two sessions. The Barratt Impulsiveness Scale (BIS; Patton, Stanford, & Barratt, 1995) was used to estimate participants' trait impulsivity.

Experimental Sessions

For the *off* session, patients with PD were in a practically defined off-state, i.e. patients discontinued their PD-related medication the evening before testing. In the *on*-session, the tests started at least one hour after the first intake of their regular medication. Both experimental sessions were conducted in the early morning, between one and two hours after waking up, to reduce the negative effects of postponing intake of the morning dose in the *off* condition. The procedure for the test sessions was the same for patients with PD and healthy controls; however, healthy controls were sometimes tested in the early afternoon. The order of *on*/*off* was randomly assigned, although due to participant drop-out this manipulation was unbalanced: Twelve patients were first tested in the *off* condition and nine first in the *on* condition. The healthy controls performed these two sessions without any intervention. However, for purposes of analysis they were assigned a dummy *on* or *off* annotation, corresponding to the order in which the matched patient performed the two sessions.

Tests were presented on a Hewlett Packard laptop running on Windows XP, using E-Prime 2.0 programming software (Psychology Software Tools Inc., Pittsburgh, PA, USA). Participants performed a Von Restorff task, and a reward-

based learning task while their EEG was recorded, and then a feedback-based learning task without EEG recording. Here, we will only report on the Von Restorff task. After finishing the experimental tests the UPDRS part III (Ramaker, Marinus, Stiggelbout, & Van Hilten, 2002) was taken. Finally, all participants again completed the BAI and BDI, to control for effects of mood and anxiety on the experimental tasks.

Von Restorff task

The Von Restorff task was modeled after that of Rangel-Gomez and Meeter (2013); but Dutch words instead of English words were used. For that purpose, two 120-word lists of concrete nouns (5-10 characters long) were constructed. Lists were constructed such that no words had the same first two letters (this was necessary for cued recall, see below). Eighty words were presented during a study phase, and 40 served as lures during a recognition phase. On each of the two sessions, participants studied one list (order counterbalanced).

In the study phase, all 80 words on one list were presented twice in a random order. Between list presentations participants could take a self-paced break. All trials started with central fixation cross with jittered presentation duration between 500-1805 ms. Subsequently, a word was presented in the middle of the screen. The word remained on the screen for 3500 ms. The font of the word was either standard or novel. See Figure 1B for example stimuli. Standard font words were always presented in Courier New font in black with 17 pixel height. Novel font words were presented in a unique color and font combination (chosen from twenty 30-pixel fonts and ten colors); these were presented in the same combination for their second presentation. The first ten words on the list were always presented in the standard font. Of the remaining 70, 50 words were presented in the standard and 20 in the novel font. Words were presented in random order and font type was randomly assigned. A 150 ms sound was presented while the word was presented at a jittered interval of 817-1790 ms (mean = 1344 ms). For 58 of 80 words, a standard sound (2.2 KHz beep) was presented for 300 ms; on the other trials, a non-familiar sound of equal duration was played (see Sambeth, Huotilainen, Kushnerenko, Fellman, & Pihko, 2006).

Participants were seated in front of the laptop in their homes; distance to the screen varied, mostly in the range of 40 to 60 cm. They were instructed to try to learn the words and ignore the sounds. After the study phase, participants immediately completed a cued recall test. The first two letters of one of the studied words were given in standard font, and the participant had to complete the word when they remembered it, or type ‘xx’ when they did not. In total, 40 words were tested, 10 of which had been presented in novel font and 30 in standard font. After completing the cued recall test, participants performed a recognition test. Here, the remaining 40 were intermixed with 40 lure words were presented one by one. Again 10 words were tested that were presented in novel and 30 that were presented in standard font. Participants had to indicate whether the word was a word from the study phase (press ‘z’) or a lure (press ‘x’).

EEG Recordings

EEG data was recorded with a 128 channel Biosemi system (Biosemi, Amsterdam, the Netherlands). Electrodes had sintered Ag/AgCl tips, and were plugged into an elastic cap (Electro-Cap International Inc. Eaton, OH, USA). For scalp electrode locations of the Biosemi system see www.biosemi.com. Data is reported from midline electrodes that correspond to the Fz, Cz, and Pz midline electrodes of the 10-20 system (equivalents in the Biosemi 128 system are: Fz = C23, xy(46,90); Cz = A1, xy(0,0); Pz = A19, xy(46,-90)). The ERP components of interest were expected to peak around these midline electrode sites since all stimuli were presented centrally, and as has been reported for similar tasks (Rangel-Gomez & Meeter, 2013; Rushby et al., 2002).

The EEG signal was digitized with a sampling rate of 512 Hz. The gain was set at 1000. During recording, electrode offset (similar to impedance in other EEG systems) was kept below 20 μV for all electrodes. Raw EEG data was digitally filtered offline using a 0.1 Hz basic finite impulse response 1000-point high-pass filter with a transition bandwidth of 0.01 Hz (roll-off 24 dB per octave), and a 40 Hz low-pass filter with a transition bandwidth of 5 Hz (roll-off 6 dB per octave). The recordings were offline referenced to the average of all EEG electrode channels (*n* = 128), in order to increase the signal-to-noise ratio by averaging out the environmental noise. Bipolar electrodes were placed at the outer corners (canthi) of the eyes as well as above and below the mid of the orbital sockets to measure horizontal (HEOG) and vertical eye movements (VEOG), such as eye blinks. These recordings were used to check whether the cleaning of eye movement components using independent component analysis (ICA) was successful.

EEG Analysis

ERPs were computed from 500 pre-stimulus to 1500 ms post-stimulus. Average peak amplitudes were computed relative to a 200 ms pre-stimulus baseline. A time-window for the P2 and P3 components was defined after visual inspection of the grand-average ERPs. The P2 was calculated for a time window of 175-250 ms, and a time-window of 400-460 ms was used for the P3. The ERPs for the main analyses were calculated only for trials of words that were later remembered (either during recall or recognition). In addition, ERPs were calculated for non-remembered words.

Noisy channels were detected by visual inspection, and replaced by the average signal of three to five surrounding channels. The data was then decomposed in independent components using the logistic infomax ICA algorithm (Bell & Sejnowski, 1995) with a natural gradient feature using the EEGlab 9.0.8.6b toolbox in Matlab (Delorme & Makeig, 2004), resulting in 128 components on basis of the 128 EEG channels. The results of the decomposition were used for the rejection of eye movements and blink components on basis of visual inspection of the components (0.8-4.6% of data was rejected per participant using ICA; that is, 1 to 6 independent components were removed). Subsequently, epochs containing extreme artifacts due to muscle tension, movements or environmental noise were rejected on basis of visual inspection by a trained individual (per condition < 5% rejected epochs). ERPs were calculated for the remainder of the data using standard signal averaging procedures (Luck, 2005). For patients with PD 4-36 (mean = 22.3) correct trials and 4-28 (mean = 17.8) incorrect trials contributed to the individual average ERPs for the novel conditions, and for healthy controls 7-36 (mean = 24.9) correct trials and 6-33 (mean = 15.4) incorrect trials were included. For the standard conditions 34-100 (mean = 70.0) correct and 18-86 (mean = 50.0) incorrect trials contributed to the individual average ERPs for patients with PD and 50-100 (mean = 78.9) correct and 18-70 (mean = 42.1) incorrect trials contributed to the individual average ERPs for healthy controls. The number of trials per condition depended on the number of remembered and forgotten words per participant and the number of trials contaminated with artifacts that were rejected.

Statistical Analyses

The performance on the Von Restorff task was analyzed with two repeated measures 2*2*2 ANOVAs with ([Type of Stimulus (Standard, Novel)]*[Type of Test (Recognition, Recall)]*[DRT (On, Off)] as within-subjects factors, and Group (Patient, Control) and a dummy variable coding which condition came first (What First; ON, OFF) as between-subjects factors. For control subjects scores on Session 1 and Session 2 were assigned to the *on* or *off* condition corresponding to the order of their matched patient, in order to investigate whether the order of conditions affected the results. For the main analyses only the main effect of What First is reported, since other interactions with this factor are meaningless for healthy

controls, and therefore impossible to interpret. To check whether coincidental order effects were present in healthy controls we also analyzed the P2 and P3 components for this group separately.

To investigate the effects of DRT on the P2 and P3 ERP components to the words during the study phase of the Von Restorff task a repeated measures 2*2*3 ANOVA with the following factors ([DRT (On, Off)]*[Stimulus (Standard, Novel)*[Electrode(Fz, Cz, Pz)]) was performed with additional between-subjects factors for which medication condition came first, What First(On, Off) and Group(Patient, Healthy Control). Only the epochs for words later remembered, either in the recall or recognition phase of the Von Restorff task, were included in these analyses.

In addition, the word-evoked P2 and P3 for remembered (defined as all correct responses in the recall or recognition phase) versus non-remembered (incorrect responses in recall or recognition) words were compared using a repeated measures 2*2*2*3 ANOVA with the factors ([Accuracy(Correct, Incorrect)]*[DRT (On, Off)]*[Stimulus (Standard, Novel)*[Electrode(Fz, Cz, Pz)]) again with between-subjects factors What First(On, Off) and Group(Patient, Healthy Control). Again, only the main effect of What First is reported. A significant interaction with Accuracy was investigated with additional ANOVAs per electrode site, and per stimulus. For these analyses only tests with Accuracy as a factor are reported. The sound-evoked ERPs are not reported in this paper, since previous findings in our lab revealed no effects for the sounds in a similar task (Rangel-Gomez & Meeter, 2013).

Results

Demographics and all mean neuropsychological test results are shown in Table 2. Results from the main statistical tests for the behavioral data and the ERP results can be found in Table 3 - in the main text we will only report *p* values of the comparisons that were theoretically interesting. Figure 2 shows mean performance on the Von Restorff task for both cued recall and recognition memory for novel and standard font words. Figure 3 shows grand-average ERPs for novel and standard font words for patients with PD and healthy controls for the *on* and *off* sessions and Figure 4 the corresponding topographic plots.

Participants Characteristics

Due to technical issues, performance scores on the Von Restorff experiment for one control participant on one session were missing. In addition, one patient with PD was excluded (male; age 57), due to a change in medication, i.e. rasagiline during the study period. Several data points were missing for the neuropsychological tests described below. This was mainly due to missing or unintelligible answers on the response sheets of the tests; different *n* is reflected in the degrees of freedom per test reported below.

With independent-samples *t*-tests patients and healthy controls were compared on their level of education and age, to check whether matching was successful. No difference was found for level of education (Verhage, 1983), $t(41) = 0.57$, $p = .569$, age, $t(1,41) = 1.12$, $p = .27$, or gender, $\chi^2(1, N = 42) = 1.62$, $p = .341$.

Patients with PD and healthy controls were then compared on their scores on the neuropsychological tests. Patients with PD and healthy controls had similar scores on the 10-word learning list, $t(41) = 1.35$, $p = .185$, Tower of Hanoi scores, $t(41) = 1.61$, $p = .115$, category fluency, $t(41) = 1.38$, $p = .175$, the Boston Naming Test, $t(40) = 1.79$, $p = .081$, and MMSE, $t(41) = 1.10$, $p = .277$ and IQ estimates derived from the NLV score were also similar, $t(41) = 0.44$, $p = .665$. On the TMT scaled scores no effect of Subtest was found, ($F < 1$), nor of Group, $F(2,42) = 1.27$, $p = .292$, $\eta^2 = .06$, nor an interaction ($F < 1$).

Groups did not differ in impulsiveness as measured by the BIS, $t(40) = 0.38$, $p = .707$, or depressive symptoms as measured by the BDI scores at screening, $t(40) = 0.75$, $p = .459$, nor in the first, $t(38) = 0.56$, $p = .579$, or second test session, $t(40) = 0.112$, $p = 0.912$. Patients scored higher on the BAI in the screening $t(41) = 2.84$, $p = .007$, and both at the first, $t(38) = 2.23$, $p = .038$, and second session, $t(40) = 2.41$, $p = .021$.

Patients had a higher UPDRS III score in the *off* (mean = 29.1) than in the *on* (mean = 21.8) session before testing, $t(20) = 5.49$, $p < .001$, indicating that the patients experienced more PD-related symptoms in the *off* compared to the *on* session. The UPDRS I, II and IV scores were 2.1, 8.1 and 4.8 respectively.

Table 2. *Demographics and mean scores on neuropsychological tests of patients with PD and healthy controls*

Demographics and Neuropsychological Test Scores	Mean Patients with PD	Mean Healthy Controls
n	21	21
Age	61.8	59.7
Gender	15 male/6 female	11 male/10 female
Education (Verhage's 7-point scale)	5.9	5.7
Test		
BDI screening	6.90 (0.86)	5.95 (0.92)
BAI screening	9.71 (1.09)	5.41 (1.06)
10WLL correct	18.43 (1.09)	20.45 (1.04)
TMT Visual Scanning Scaled	10.43 (0.62)	11.00 (0.60)
TMT Number Sequencing Scaled	10.00 (0.76)	11.50 (0.45)
TMT Letter Sequencing Scaled	9.86 (0.84)	11.09 (0.49)
TMT Number/Letter Sequencing Scaled	10.71 (0.78)	11.77 (0.47)
TMT Motor Speed Scaled	9.33 (0.72)	10.41 (5.17)
Tower of Hanoi Scaled	10.57 (0.52)	11.68 (0.46)
BIS Score	59.25 (1.43)	58.27 (2.09)
Boston Naming Task	163.50 (1.29)	167.09 (1.51)
Category Fluency	26.33 (1.38)	29.05 (1.40)
MMSE	28.81 (0.34)	28.23 (0.41)
NLV	88.67 (2.91)	91.50 (2.24)
IQ Estimation (on basis of NLV Score)	113.57 (3.02)	115.23 (2.34)

Standard errors in parentheses. BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; 10WLL = Ten Word Learning List; TMT = Trail Making Test; BIS = Barratt Impulsiveness Scale; MMSE = Mini Mental State Examination; NLV = Nederlandse Leesvaardigheidstest (Dutch reading skills test).

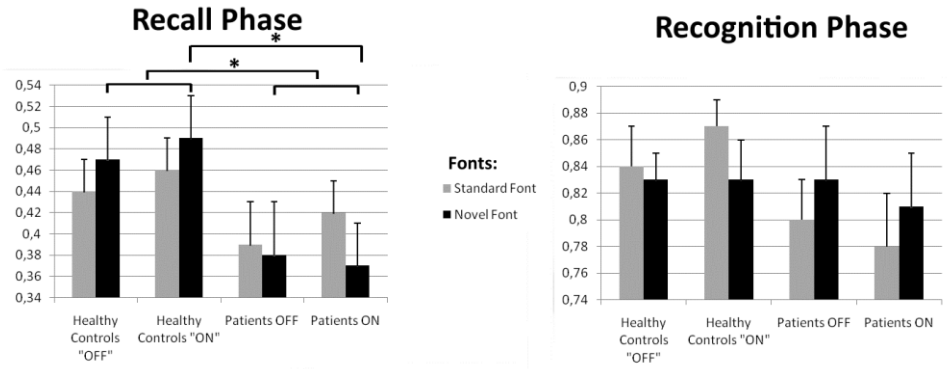


Figure 2. *Mean proportion of correctly remembered words for recall and recognition on the Von Restorff task. Error bars reflect standard errors.*

Behavioral data Von Restorff task

Performance was better for recognition than for recall, $p < .001$. None of the other within-subjects factors had a main effect; in particular, there was no overall difference between novel and standard words, $p = .87$. There was a trend, however, towards lower scores for patients with PD than controls, $p = .079$. No main effect of What First was found ($F < 1$).

Type of Test, Stimulus, and Group interacted, $p = .031$. The effects of Stimulus and Type of test were different for patients and controls: Whereas healthy controls recalled more novel than standard font words, but recognized more standard words, patients with PD showed exactly the opposite pattern. They recalled more standard than novel font words, and recognized more novel font words. This interaction was further investigated by repeating the ANOVAs separately for novel font and standard font words. It turned out that words presented in novel fonts drove the interaction: Type of Test and Group for words presented in novel fonts interacted, $F(1,40) = 4.19$, $p = .047$, $\eta^2 = .10$; patients recalled fewer novel font words than controls, with no difference between groups in recognition of novel font word. No interactions between Type of Test and Group were found for standard font words ($F < 1$). Notably, this effect was independent of medication, as no interaction with DRT was significant.

The sounds, included to provide an independent measure of novelty processing, did not yield any novelty-related effects in patients nor controls, which corresponds with findings of Rangel-Gomez, Hickey, & Meeter (2013). Therefore, this manipulation will therefore not be further discussed.

Word-evoked P2

The P2 was generally larger for words presented in novel fonts, than for words presented in standard font, $p < .001$. There was no main effect of DRT ($F < 1$), nor of Group or What First ($F < 1$). P2 amplitude varied over the electrode sites, $p = .009$. It was larger at Cz than at Fz , $F(1,39) = 12.30$, $p = .001$, $\eta^2 = .24$, and did not differ between electrodes Cz and Pz ($F < 1$).

Group and DRT interacted, $p = .039$, with larger P2 decrements for patients appearing in the *off* than in the *on* session. To examine this interaction we performed two 2*2*3 repeated measures ANOVA with the factors ([Stimulus (Standard, Novel)]*DRT(On, Off)*[Electrode(Fz, Cz, Pz)]) and between-subjects factors What First for the patients with PD

and the healthy controls separately. There were no differences in P2 in the *on* versus the *off* session in patients with PD ($F < 1$), but a trend for a larger P2 *off* versus *on* in healthy controls, $F(1,20) = 3.96$, $p = .060$, $\eta^2 = .17$. Since there was no DRT manipulation in healthy controls this difference must have resulted from random noise, but it was the major contributor to the DRT*Group interaction.

To investigate whether the P2 correlated with subsequent memory, we compared the P2 evoked by words that were later remembered versus those that were not (see Figure 6 for grand-average ERPs for remembered and non-remembered standard and novel font words). There was no main effect of Accuracy ($F < 1$), but it interacted with Electrode and Stimulus, $p = .008$. This interaction was further examined with separate ANOVAs per electrode site, with 2*2*2 repeated-measures ANOVAs with factors ([Accuracy(Correct, Incorrect)]*[DRT (On, Off)]*[Stimulus (Standard, Novel)]) and between-subjects factors What First and Group. The interaction Accuracy and Stimulus was only significant at Pz, $F(1,39) = 5.34$, $p = .026$, $\eta^2 = .12$ and not at Fz, and Cz ($F < 1$). At this electrode, the P2 was larger for correctly remembered than for non-remembered words, and this effect was stronger for the words presented in novel font than in standard font.

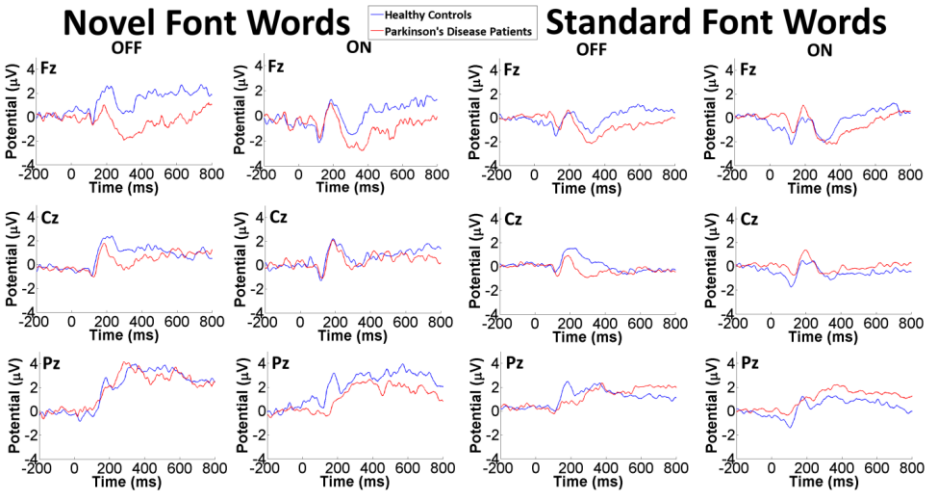


Figure 3. *Grand average ERPs for healthy controls and patients with PD for correctly remembered words. ERPs for novel font words for the off session (panel A) and for the on session (panel B), and for standard font words for the off session (panel C), and the on session (panel D). Note, on/off for healthy controls does not reflect a manipulation of DRT, but an assigned session corresponding to corresponding to the order in which the matched patient performed the two sessions. Electrode locations include Fz, Cz, and Pz.*

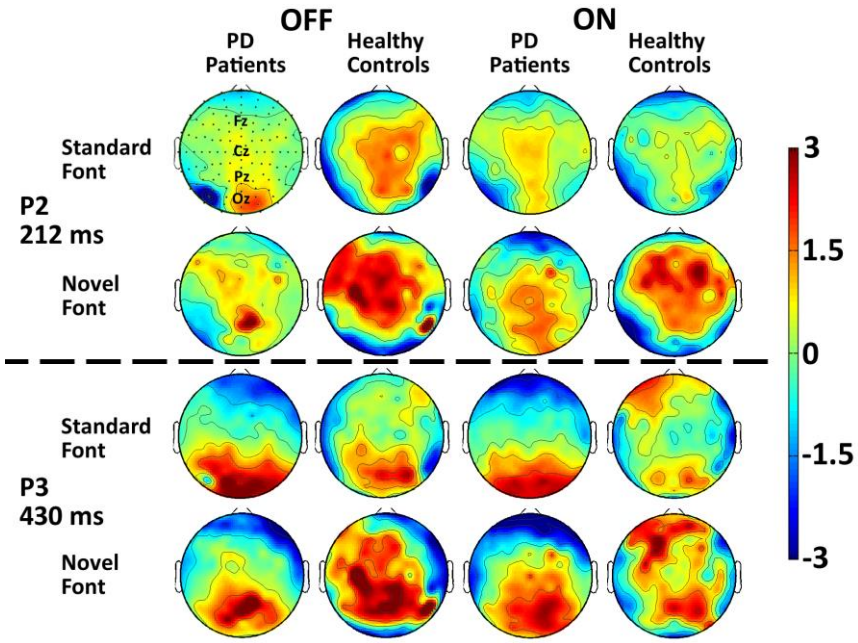


Figure 4. *Topographic plots for the grand-average standard and novel font P2 and P3 components for patients with PD and healthy controls on and off medication for correctly remembered words. Data is shown for all 128 EEG electrodes, and reflects peak amplitude at 212 ms for the P2 and 430 ms for the* P3.

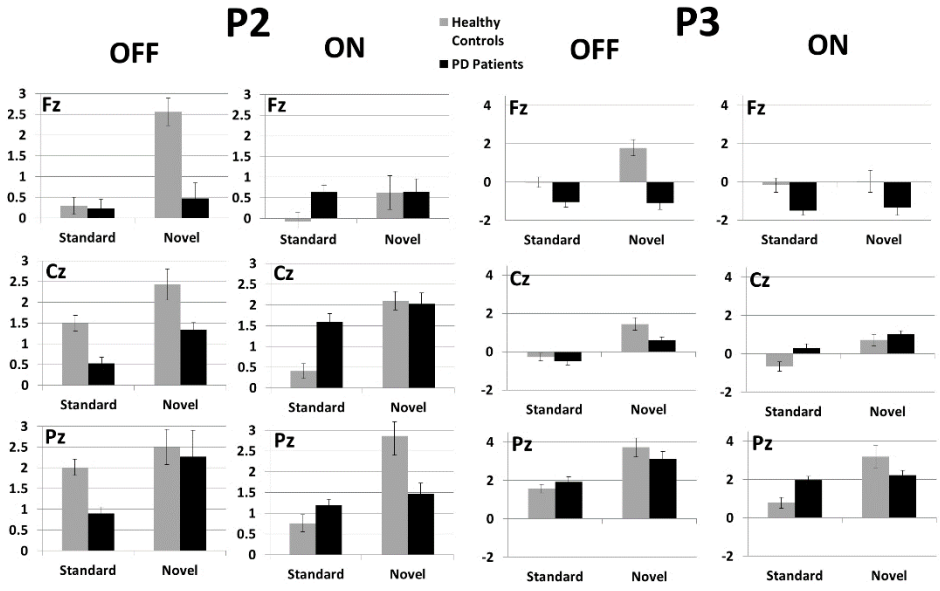


Figure 5. *Mean ERPs for correctly remembered words for A) the P2 (175-250 ms) and B) P3 (400-460 ms) time-windows at electrodes Fz, Cz, and PZ for healthy controls and patients with PD. Error bars reflect standard errors.*

Word-evoked P3

The P3 was investigated with the same repeated-measures ANOVA as the P2 component. Like the P2, the P3 was generally larger for novel font words than for standard font words, $p < .001$. There was no main effect of DRT, $p = .175$, nor of Group, $p = .209$, or What First ($F < 1$). Electrode site affected the P3 amplitude, $p < .001$. The P3 peaked posteriorly: it was larger at Pz than at Cz, $F(1,39) = 27.85$, $p < .001$, $\eta^2 = .42$, with a trend towards a larger P3 at Cz than at Fz, $F(1,39) = 3.51$, $p = .069$, $\eta^2 = .08$.

Stimulus and Group interacted, $p = .026$: The effect of Stimulus (a larger P3 for novel than standard font words) was more pronounced for healthy controls than for patients. No other interactions were significant.

As for the P2, we compared the P3 for remembered and non-remembered words. There was no main effect of Accuracy ($F < 1$), but it interacted with Electrode, $p = .028$, with the largest differences between remembered and non-remembered trial at Pz. In addition, Accuracy interacted with Electrode and Stimulus, $p = 005$. This interaction was further investigated with separate ANOVAs per electrode site (the same as used for the P2). There were statistical trends for the interaction between Accuracy and Stimulus at Fz, $F(1, 41) = 3.23$, $p = .08$, $\eta^2 = .07$, and Pz, $F(1,41) = 3.99$, $p = .052$, $\eta^2 = .09$, but not at Cz ($F < 1$). Additional ANOVAs for novel and standard font words separately showed that the interaction at Pz was mainly driven by the novel font words, with a larger P3 for remembered than for forgotten novel font words, $F(1,41) = 6.02$, $p = .019$, $\eta^2 = .13$, and no differences for standard font words, $F(1,41) = 1.73$, $p = .196$, $\eta^2 = .04$. This effect was reversed at Fz, with a larger P3 for non-remembered than remembered novel font words, $F(1,41) = 8.26$, $p = .006$, $\eta^2 = .17$, and again no differences for standard font words, $F < 1$.

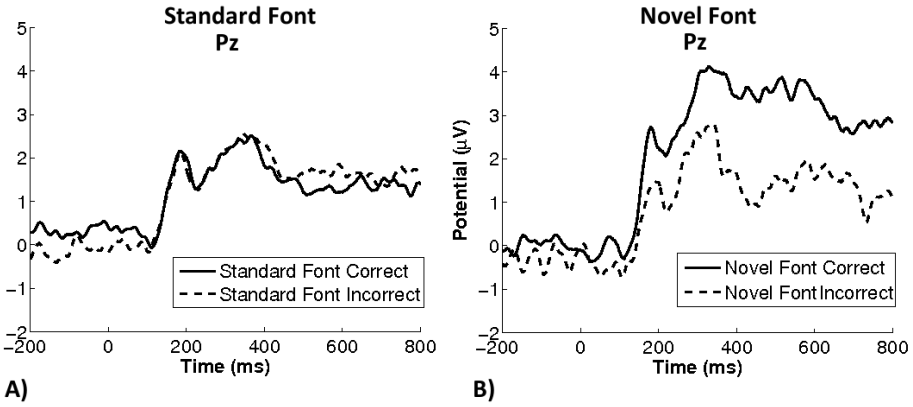


Figure 6. *Grand-average ERPs for remembered (correct) and non-remembered (incorrect) words for A) standard and B) novel font words. Data depicted here is collapsed over DRT and Group.*

Discussion

The present study's goal was to investigate the processing and learning of novel information in patients with PD compared to healthy controls. In addition, the effects of dopamine on these processes was investigated. In one session, patients with PD were tested on DRT, just after intake when levels of dopamine are optimal. In the other session the patients were tested after overnight withdrawal, when dopamine is relatively depleted. The healthy controls, matched on several important variables, were also tested twice.

Recall was impaired in patients with PD, but no group differences were found for the recognition phase. This dissociation between impaired recall and relatively spared recognition is in line with numerous studies (Brown, & Marsden, 1987; Buytenhuijs et al., 1994; Fischer et al., 1990; Helkala et al., 1988; Mohr et al., 1989; Sagar et al., 1988; Sullivan & Sagar, 1989; Taylor et al., 1986; Tweedy et al., 1982; Weingartner et al., 1984). Impaired recall in patients with PD could be caused by weaker encoding or disturbed retrieval (Dunlosky et al., 2000; McDaniel, Dornburg, & Guynn, 2005; Schmidt, 1991). Although our findings of spared recognition favor a deficit at retrieval rather than at encoding (Bosboom, Stoffers, & Wolters, 2004; Brown & Marsden, 1990; Flowers, Pearce, & Pearce, 1984; Weingartner et al., 1984), our findings of P2 and P3 decrements for patients with PD are in favor of a disruption at encoding. These two observations suggest that both encoding and retrieval of newly learned information is altered in patients with PD.

Both groups were tested on the Von Restorff task, but only healthy controls showed the typical von Restorff effect (i.e. better memory for distinctive items) during recall, while no effect was found during recognition (Fabiani & Donchin, 1995; Rangel-Gomez & Meeter, 2013). These effects were reversed for patients with PD, who had better memory for standard than novel font words during recall and better memory for novel than standard font words during recognition. These results suggest that the processing of novelty is altered in patients with PD. Evidence for this suggestion is found in the ERP results. The P3 component for novel compared to standard font words was smaller for patients with PD than for controls. As the P3 peaked posteriorly, we interpret it as a P3b component.

The visual P2 component is related to encoding of words (Dunn, Dunn, Languis, & Andrews, 1998), and is considered an index of differential stimulus processing during elaborative learning of words, since its amplitude predicted recall (Rushby et al., 2002). In the present study, P2 amplitude was larger for novel than for standard font words, and it correlated with later retrieval specifically for novel font words: Novel font words that were later remembered evoked a larger P2 than words that were not correctly remembered. The P3b has also been associated with memory processes (Polich, 2007) and was also larger for words that were subsequently remembered. This suggests that patients processed the novel words in a different way than healthy controls. Patients with PD may apply an encoding strategy that allows them to recall standard font words at the same level of accuracy as healthy controls, but makes it harder to retrieve novel font words. Such differences in recall strategy would explain the otherwise puzzling finding that while healthy controls recall more novel font words and recognize more standard font words (replicating earlier studies), patients with PD recalled less novel font words but yet recognized more of them. Remarkably, none of these effects were affected by DRT. Several types of memory have been found to be facilitated by DRT, such as learning associations between pictures and artificial pseudowords in healthy individuals (Knecht et al., 2004), verbal memory in PD (Mohr et al., 1989), object recognition (Righi, Viggiano, Paganini, Ramat, & Marini, 2007), and motor memory formation in elderly (Floel et al., 2008). Also in healthy young adults a challenge with dopamine agonist apomorphine has been shown to lead to a specific increase in recall of novel font words (Rangel-Gomez et al., 2013). In contrast, we did not observe any effects of medication on recall or recognition, nor on ERP components associated with novelty processing.

A possible explanation for the null effect of DRT may be found in the fact that the alterations in dopaminergic brain circuits in PD are not equal across the whole brain. In three relatively independent circuits, the dorsal striatum (e.g. dorsal putamen) and the dorsal caudate nucleus receive input from the SN, and the ventral striatum is innervated by dopamine cells in the VTA (Floresco & Grace, 2003; Humphries & Prescott, 2010; Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004; Vriend et al., 2014). These three corticostriatal circuits (Alexander, DeLong, & Strick, 1986; Rosvold, 1972) can also be functionally dissociated (Dias, Robbins, & Roberts, 1996): The SN is connected to the dorsolateral prefrontal loop (the associative circuit), and in a separate pathway to the premotor cortices (the motor circuit), and the ventral striatum to the orbitofrontal loop (the limbic circuit; Vriend et al., 2014). In PD, degeneration of dopamine cells is generally more severe in the SN than in the VTA, where degeneration occurs mainly in later stages of the disease (Djaldetti et al., 2011; Fearnley & Lees, 1991; Kish, Shannak, & Hornykiewicz, 1988). As a result, in the early stages of PD dopamine

depletion is more profound in the more dorsal parts of the basal ganglia, whereas the more ventral areas (such as the ventral putamen, and nucleus accumbens) become more profoundly affected in later stages (Agid et al., 1993; Kish et al., 1988). This in turn means that the effect of DRT on cognitive functioning in PD is not uniform over all domains. Presumably DRT supplies dopamine in some depleted areas (thereby for example remediating motor symptoms) in early PD, while overdosing other circuits that are not as strongly affected yet – having a potentially detrimental effect (Agid et al., 1993; Gotham, Brown, & Marsden, 1988; Kish et al., 1988; Swainson et al., 2000b). Since the hippocampus and surrounding medial temporal cortex interact more closely with the ventral than with the dorsal striatum (Bunzeck, Guitart-Masip, Dolan, & Düzel, 2011; Houk, 2005; Macdonald & Monchi, 2011), dopamine overdosing could also affect functions relying on the medial temporal lobe such as novelty detection and memory encoding. Several studies have suggested that DRT indeed can have adverse effects on learning (Cools, Barker, Sahakian, & Robbins, 2001; Mehta, Swainson, Ogilvie, Sahakian, & Robbins, 2001; Swainson et al., 2000a), and can selectively impair recall in patients with moderate PD compared to healthy controls, and impair performance *on* compared to *off* medication (Edelstyn, Mayes, Denby, & Ellis, 2012; Edelstyn, Shepherd, Mayes, Sherman, & Ellis, 2010). Our sample may have contained both patients in whom DRT produces such 'overdosing', and patients in whom DRT ameliorated memory. This would also explain the overall lack of effects of DRT in the present study.

Alternatively, other brain abnormalities may explain part or all of the impairment. The Lewy bodies that characterize PD can be found throughout the brains of patients, resulting in diffuse brain damage that may explain part of the cognitive dysfunctions seen in the disease. As a function either of local cortical damage (Gibb, Luthert, Janota, & Lantos, 1989) or secondary to basal ganglia dysregulation, frontal dysfunction is common in Parkinson's disease (Lewis et al., 2003). Such dysfunction may explain the general learning deficit in patients with PD. However, patients were not-demented (MMSE > 24) and scored at similar levels as the matched controls on the neuropsychological tests measuring frontal lobe functioning (i.e. the Tower of Hanoi, TMT, and the category fluency test), suggesting that our findings cannot be explained by a general frontal deficit.

The present study has some limitations. LEDD was taken as a measure of dopamine status; however, the level of depletion between patients also depends on the type of DRT, the level of degeneration, regional differences within the striatum, and the amount of endogenous dopamine available in addition to the amount of suppletion by DRT. Nevertheless, it can be assumed that dopamine levels were higher in the *on* than in the *off* session. Matching was successful on the main selection criteria, but patients experienced more symptoms associated with state anxiety in the week preceding the sessions than healthy controls. Possibly, peripheral symptoms associated with PD contributed to this effect, because some BAI items query experiences that are similar to the motor and autonomic symptoms of PD (e.g., having a numb or tickling sensation, trembling/shaking legs, dizziness in the head, instability, and feeling weak), but the possibility that patients experienced higher anxiety cannot be ruled out. Another weakness is that due to the large amount of factors a large number of tests were performed. We base our conclusions only on a selection of the analyses; nonetheless, some effects would not survive corrections for multiple comparisons, suggesting that the study was possibly underpowered. Nonetheless, we could link behavioral performance to psychophysiological indices, and both suggested that novelty processing is reduced and recall memory is impaired in patients with PD, supporting the validity of our findings. Another limitation is that patients with PD are known to have impaired cognitive flexibility (Cools, Barker, Sahakian, & Robbins, 2001). Possibly switches in font and color may have distracted the patients, interfering with encoding. However, if such distraction occurred it would have impaired both recall and recognition, which was not the case.

Conclusion

In sum, both the P2 and P3 ERP components were larger for novel than standard font words, and their amplitude correlated with memory performance, especially for novel font words. Irrespective of DRT, patients with PD had a smaller

P3 for novel compared to standard font words than healthy controls, suggesting that novelty processing during encoding was reduced in the patients. In line with these psychophysiological findings, healthy controls showed the typical Von Restorff effect, better memory for novel font words, while patients with PD showed the reverse effect, better recall for standard font words. Moreover, patients with PD generally recalled less words than healthy controls. Taken together these results suggest that novelty processing and memory encoding are impaired in PD. Dopamine did not significantly affect these processes, possibly by overdosing the involved brain areas.